**REMARKS**

I. *Introduction*

Claims 1-3, 6-12, 14-21, and 25-28 are pending. Claims 1-3, 6-9, 15-17, and 19 have been amended and claims 25-28 are new. Claims 4, 5, 13, 23, 18, 22, and 24 have been cancelled without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of the cancelled claims in one or more continuing applications.

Support for the amendments to claim 1 and for new claims 25-27 may be found, *inter alia*, in claims 4 and 17 and in the Specification at page 16, lines 4-9. Support for new claim 28 may be found, *inter alia*, in Example 5, on page 43 of the Specification. No new matter has been introduced by way of any of the foregoing amendments to the claims.

II. *Examiner Interview*

The undersigned and the Applicants wish to thank Examiners Schlientz and Sheikh for the cordial and productive interview of July 14, 2008. The Examiners' helpful comments and suggestions were instrumental in preparing this response. During the interview, Applicants' representatives, inventor Roman Rariy, and the Examiners discussed the differences between the claimed invention and the inventions described in the art of record, and, accordingly how the present invention is novel and non-obvious over the same art. In consultation with the Examiners, Applicants' representatives agreed to amend the claims such that, *e.g.*, there is a discrete lag time between a first and a second pulse.

I. *The rejections under 35 U.S.C. § 103(a) should be withdrawn*

Claims 1-4, 6-10, 15-17, and 19-22 stand rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,340,476 to Midha *et al.* (hereinafter "Midha") in view of Marc Ansseau *et al.*, *Controlled comparison of milnacipran and fluoxetine in major depression*, 114 *Psychopharmacology* 131-137 (1994) (hereinafter "Ansseau") for the reasons set forth on page 2 of the Advisory Action dated January 31, 2008. Claims 1-4, 6-10, and 15-22 stand rejected under 35 U.S.C. § 103(a) over Midha in view of Ansseau and further in view of Matthew A. Menza *et al.*, *Modafinil Augmentation of Antidepressant Treatment in Depression*, 61 *J. Clin. Phsychiatry* 378-381 (2000) (hereinafter "Menza") for the reasons set forth on page 2 of the Advisory Action dated January 31, 2008. Claims 1-12, 15-17, and 19-22 stand rejected under 35

U.S.C. § 103(a) over Midha in view of Ansseau and further in view of U.S. Patent No. 6,699,506 to Paillard *et al.* (hereinafter "Paillard") for the reasons set forth on page 2 of the Advisory Action dated January 31, 2008. Finally, claims 1-3, 6-17, and 20 stand rejected under 35 U.S.C. § 103(a) over Published U.S. Application No. 2003/0203055 to Rao *et al.* (hereinafter "Rao") for the reasons set forth on page 2 of the Advisory Action dated January 31, 2008.

Claim 1, as amended, is directed to a milnacipran formulation that provides pulsatile release of milnacipran wherein the formulation comprises an immediate release dosage unit; a first delayed release dosage unit; and optionally a second delayed release dosage unit. The immediate release dosage unit comprises a first dose of the active agent that is released substantially immediately following oral administration of the dosage form to a patient resulting in a first plasma level peak at a time between approximately 0.05 hours to **less than** 3 hours following oral administration. The first delayed release dosage unit comprises a second dose of the active agent resulting in a second plasma level peak at a time of **more than** 3 hours to less than 14 hours following oral administration of the dosage form. Finally, the second delayed release dosage unit, when present, comprises a third dose of the active agent resulting in a third plasma level peak at a time between approximately 5 hours to less than 18 hours following oral administration of the dosage form. The milnacipran formulation that provides the pulsatile release of milnacipran exhibits, *e.g.*, a lag time during which there is no release of the drug between the release of the first dose in less than 3 hours and the second dose in more than 3 hours. The lag time is followed by a rapid drug release from the first delayed release dosage unit. *See* Specification at page 16, lines 4-9 for the definition of "pulsatile release dosage form."

As set forth in greater detail below, far from providing one of ordinary skill in the art with a reason to prepare a formulation as claimed, the prior art actually teaches away from the invention by disclosing the delivery of lipophilic drugs, such as methylphenidate, in areas of the gastrointestinal tract where drugs that are lipophilic would be expected to be absorbed. More particularly, at the time the invention was made, one of ordinary skill in the art would not have been motivated to release a drug such as milnacipran, which is lipophobic, in areas of the gastrointestinal tract where only lipophilic drugs would be expected to be absorbed. Moreover, one of ordinary skill in the art would not have expected for a lipophobic drug to be 100% absorbed in that area of the gastrointestinal tract.

Midha teaches pharmaceutical dosage forms for pulsatile delivery of methylphenidate. The dosage forms are comprised of first, second and optionally third dosage units, with each dosage unit having a different drug release profile. Midha, abstract. Midha teaches that the pharmaceutical dosage forms provide for pulsatile delivery of methylphenidate. *Id.* at col. 4, lines 42-44. According to Midha, "pulsatile" means that a plurality of drug doses are released at spaced apart time intervals. *Id.* at col. 4, lines 44-45. Upon ingestion of the dosage form, release of the initial dose is substantially immediate, *i.e.*, the first drug release "pulse" occurs within 1-2 hours of ingestion. *Id.* at col. 4, lines 46-48. The initial pulse is followed by a first time interval during which substantially no drug is released from the dosage form, after which a second dose is then released. *Id.* at col. 4, lines 48-51. According to Midha, the second dose is released on the order of 3-5 hours following ingestion of the dosage form. *Id.* at col. 4, lines 51-53. The release of the second dose is followed by a second non-release interval, which is again followed by a "pulse" of drug release. *Id.* at col. 4, lines 53-55. According to Midha, the release of the third dose occurs on the order of 7-9 hours following ingestion. *Id.* at col. 4, lines 55-57.

The release profile for Midha's pulsatile delivery of methylphenidate can be illustrated as shown below in Figure 1.

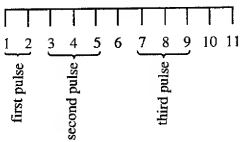


Figure 1

It is well accepted that under fasted conditions, one hour after ingestion of a drug dosage form one would expect the dosage form to be in the stomach. Ian R. Wilding and David V. Prior, *Remote Controlled Capsules in Human Drug Absorption (HAD) Studies*, 20 *Therapeutic Drug Carrier Sys.* 405, 420 (2003); submitted herewith as Exhibit 1. After about two hours, one would expect the drug dosage form to be in the jejunum of the small intestine. *Id.* After about three hours after ingestion, one would expect the drug dosage form to be in the ileum of the small intestine. *Id.* After about five hours, one would expect the drug dosage form to be exiting

the ileocolonic junction (ICJ) and entering the colon. *Id.* At seven to nine hours post-ingestion, one would expect the drug dosage form to still be making its way through the colon. *Id.* Under fed conditions, the times given above following the time spent in the stomach would be offset by about two hours, since it is well known that the residence time of food in the stomach is about two hours. *See, e.g.*, EP0202159A2, page 7, lines 2-7; submitted herewith as Exhibit 2. Thus, for example, under fed conditions, the drug dosage form would be expected to be exiting the ICJ and entering the colon after about seven hours.

As mentioned above, methylphenidate is known to be lipophilic. *See* http://uuhsc.utah.edu/pharmacy/bulletins/NDB_112.pdf, attached hereto as Exhibit 3. It is also known that lipophilic drugs such as methylphenidate absorb well colonically. *See, e.g., Alza Corp. v. Mylan Labs. Inc.*, 80 U.S.P.Q.2d 1001, 1006 (Fed.Cir. 2006) ("The relationship between the physical characteristics of a drug and its colonic absorption is not yet clear but studies in the rat suggest that lipophilic drugs are well absorbed along the length of the gastrointestinal tract, whereas hydrophobic polar drugs are absorbed much less from the colon than from the small intestine."), attached hereto as Exhibit 4.

Based on the foregoing, the person of skill in art would have had a reasonable expectation that a **lipophilic** drug such as Midha's methylphenidate, or any drug for that matter, would be entering the colon five hours post ingestion. The person of skill in the art would also expect that such a lipophilic drug would be colonically absorbed. Accordingly, the skilled artisan would have been motivated to produce the pulsatile drug dosage form that is taught by Midha to deliver a lipophilic drug that is absorbed as far down the gastrointestinal tract as the colon. Applicants assert, however, that the person of skill in the art **would not** have a reasonable expectation that a drug such as milnacipran, which is **lipophobic**,[1] would be colonically absorbed and certainly not as well as the inventors observed.

[1] *See* G. Neliat *et al.*, *Lack of Effect of Repeated Administration of Milnacipran, a Double Noradrenaline and Serotonin Reuptake Inhibitor, on the β-adrenoceptor-linked Adenylate Cyclase System in the Rat Cerebral Cortex*, 35 *Neuropharmacology* 589, 592 (1996); and Daisuke Mochizuki *et al.*, *Repeated administration of milnacipran induces rapid desensitization of somatodendritic 5-HT$_{1A}$ autoreceptors but not postsynaptic 5-HT$_{1A}$ receptors*, 16 *Journal of Psycopharmacology* 253, 258 (2002); attached as Exhibits 5 and 6, respectively.

As shown in Figure 2 on page 36 of the Keller declaration filed on January 3, 2008 (attached hereto as Exhibit 7), after about six to ten hours, the plasma concentration of milnacipran surprisingly and unexpectedly reaches a maximum level indicating that milnacipran is still being absorbed six to ten hours post-ingestion. At this point, the milnacipran in the claimed formulation would be in the colon (regardless of fed or fasting conditions)—an area of the gastrointestinal tract where one would not expect absorption of a lipophobic drug like milnacipran. Surprisingly and unexpectedly the inventors observed about 100% absorption of the pulsed dose of milnacipran in the colon, where the second or third delayed release dosage units would be expected to be six to ten hours post-ingestion. These results are surprising and unexpected because the skilled artisan would not have expected a lipophobic drug to (a) be absorbed in the colon; and (b) be absorbed in the colon to such a high extent.

Neither Ansseau nor Menza nor Paillard remedies the deficiencies in Midha. Ansseau describes the efficacy and tolerance of milnacipran relative to the efficacy and tolerance of fluoxetine in the treatment of depression. Menza describes the use of modafinil to augment antidepressant treatment. Finally, Paillard teaches pharmaceutical compositions with prolonged release for the oral administration of milnacipran. But, neither Ansseau nor Menza nor Paillard teaches the pulsatile delivery of drug dosage forms. Moreover, both fluoxetine and modafinil are hydrophobic (*i.e.*, lipophilic) drugs. *See, e.g.*, Federico Momo *et al.*, *Interaction of fluoxetine with phosphatidylcholine liposomes*, 118 *Biophysical Chemistry* 15, 25-21 (2005) and Published PCT Appl. No. WO05/004917 for fluoxetine and modafinil, respectively. Accordingly, Midha, alone or in combination with Ansseau, Menza, and/or Paillard, does not teach the delivery of lipophobic drugs such as milnacipran in a pulsatile fashion as presently claimed. Applicants therefore respectfully request that the rejections of the claims over Midha, alone or in combination with Ansseau, Menza, and/or Paillard, be withdrawn.

Applicants also respectfully request that the rejection of claims 1-3, 6-17, and 20 over Rao be withdrawn. Applicants reiterate that, contrary to the Examiner's assertions, Rao does not teach the delivery of milnacipran in a pulsatile fashion as presently claimed. The multilayer tablet that the Examiner describes in the Advisory Action dated January 31, 2008 will deliver milnacipran in a continuous fashion without any lag time between the delivery of the immediate release portion of the tablet and the sustained release portion of the tablet. As discussed on page

16, lines 4-9, of the Specification, a pulsatile release profile is characterized by a time period of no release (lag time) followed by rapid drug release.

In sum, therefore, (1) the invention is not *prima facie* obvious because the prior art would have directed one of ordinary skill in the art away from using a lipophobic compound such as minalcipran in a pulsatile formulation as claimed where at least one of the drug releases takes place, at least partially, in the colon; and (2) even if the prior art is viewed as not providing a teaching away from the invention, it was certainly unexpected that a lipophobic compound such as minalcipran would not only absorb in the colon, but at 100%.

Applicant respectfully submits that the pending claims are in condition for allowance. The Examiner is respectfully urged to contact the undersigned telephonically if she believes that it will expedite the allowance of the pending claims.

Respectfully submitted,
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